Peak postoperative troponin levels outperform preoperative cardiac risk indices as predictors of long-term mortality after vascular surgery

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Abstract

Background: The utility of postoperative troponins as an independent predictor of long-term mortality after vascular surgery is unknown.

Methods: One hundred sixty-four consecutive patients underwent vascular surgery and postoperative mortality was determined at 2.5 years. Troponins were drawn within 48 hours postsurgery and the peak levels, defined by the upper reference limit (URL), were categorized as negative (<URL), low positive (\(\geq\)URL but <3 times the URL), or high positive (\(\geq\)3 times the URL). A logistic regression model comprised all univariate predictors of long-term mortality and included peak troponin levels and the number of the preoperative revised cardiac risks.

Results: Mortality in the high positive (n = 44), low positive (n = 41), and negative (n = 79) troponin groups was 46%, 17%, and 6%, respectively (\(P < .05\)). Independent predictors of long-term mortality were peak postoperative troponins (odds ratio [OR], 8.85; 95% confidence interval [CI], 3.29-23.81; \(P < .001\)), tissue loss (OR, 2.87; 95% CI, 1.03-8.00; \(P = .043\)), and use of statins (OR, 0.19; 95% CI, 0.07-0.49; \(P < .001\)). The \(c\) index for peak troponin levels was 0.75 (95% CI, 0.68-0.82; \(P < .01\)) and outperformed the Revised Cardiac Risk Index for predicting long-term outcomes.

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Conclusions: Among patients undergoing vascular surgery, an elevated postoperative troponin level provides incremental value in predicting long-term outcomes, when compared with standard preoperative cardiac and surgical risks.

Although patients undergoing vascular surgery are at increased risk of cardiovascular complications, a strategy of preoperative coronary artery revascularization is not recommended for most patients undergoing elective vascular surgery [1]. Improving outcomes in this high-risk patient group undergoing noncardiac operations will require novel strategies to address risk factor modification in the postoperative period. The potential value of serial troponin assays as a surveillance biomarker after major noncardiac operations is gaining widespread acceptance [2]. Although a peak troponin I level above the upper reference limit (URL) or the 99th percentile of a normal population is associated with a higher risk of death [3-5], the utility of troponin assays as an independent predictor of long-term outcome among patients undergoing vascular surgery has been uncertain [6]. Patients with advanced arterial occlusive disease and tissue loss tend to have a higher long-term postoperative risk of death, and their poor outcomes may be a result of factors independent of the cardiac risk profile [7]. To test whether an elevated peak troponin level provides incremental value in predicting long-term postoperative outcomes compared with standard preoperative clinical variables, we analyzed data from consecutive patients undergoing vascular surgery. We hypothesized that a peak troponin level at greater than or equal to 3 times the URL of the specific troponin assay would be an optimal discriminator of outcomes, compared with standard preoperative clinical risk variables, as enumerated by the Revised Cardiac Risk Index (RCRI) [8]. Because perioperative use of statins protects in the early period after vascular surgery [9], we also tested whether statin use at the time of discharge would also predict long-term outcomes. Consideration of a higher threshold for an elevated peak cardiac biomarker is rational, based on the Consensus Statement from the Combined Task Forces on the Redefinition of a Myocardial Infarction (MI), which have recommended a high threshold of greater than or equal to 3 times the URL of troponins when considering the diagnosis of a procedural-related MI after coronary artery revascularization with either percutaneous coronary interventions or coronary artery bypass graft surgery [10].

1. Methods

1.1. Study cohort

The Institutional Review Board at the Minneapolis Veterans Affairs Medical Center approved the study. In the present cohort, we analyzed 164 consecutive patients undergoing vascular surgery between January 2005 and December 2007 and determined long-term outcomes based on presenting preoperative cardiac risk variables, perioperative vascular surgical characteristics, and postoperative cardiac troponin levels.

1.2. Troponin assays

Blood was obtained in all patients in the first 2 days after vascular surgery, and the troponin I levels were measured by the Dade Behring Dimension Analyzer. The peak troponin I level was considered abnormal if it exceeded the URL, based on the 99th percentile of a normal population, as specified by the manufacturer guidelines. The lower limit of detection was 0.03 μg/L, and the 20% and 10% total imprecisions were determined at 0.1 and 0.3 μg/L, respectively. The 99th percentile normal reference concentration of the cardiac troponin I assay was predetermined at lower than 0.1 μg/L [11]. Those values that exceeded the URL were categorized as either low (+; ≥ URL but <3 times the URL) or high (+; ≥3 times the URL).

1.3. Outcomes

Long-term survival was determined from the time of the vascular operation and was retrieved through the BIRLS system (the Department of Veterans Affairs Beneficiary Information and Electronic Records Locator Subsystem).

1.4. Statistics

Continuous variables demonstrating a normal distribution are expressed as mean ± SD, and discrete variables are presented as frequencies and percentages. Continuous variables were compared between groups using the unpaired Student t test for normally distributed data or the Mann-Whitney U test for nonnormally distributed data. Proportions were compared with the χ² test. Medcalc version 11.3 (Mariakerke, Belgium) was used for statistical analysis.

Clinical variables that might be associated with increased mortality at 2.5 years after vascular surgery were determined for all patients and included preoperative cardiac risk factors, perioperative vascular surgical variables, and postoperative troponin levels. A logistic regression model was created based on significant predictors of outcome and included preoperative cardiac risks, as estimated by the RCRI (≥3 risks) [8,12], advanced arterial occlusive disease...
(tissue loss with nonhealing ulcers) [7,13], peak postoperative troponin levels (≥3 times the URL of the specific troponin assay) [10], and perioperative use of statins [9]. Odds ratios (OR) and 95% confidence intervals (CIs) are reported from this analysis. Receiver operating characteristic curves were also generated to assess how well either the peak troponin levels or the RCRI discriminate between survival and nonsurvival. The c index (area under the curve) and the 95% confidence intervals were provided for each parameter. All tests were 2-sided, with significant differences defined as $P < .05$.

2. Results

Of the 164 patients, 32 (19.5%) died within 2.5 years of the operation. Eighty-five (51.8%) had a peak postoperative troponin value that exceeded the URL, and their long-term mortality was increased 36.4% compared with 6.3% in the 79 patients with a negative peak troponin level ($P < .05$). A peak postoperative troponin level that was greater than or equal to 3 times the URL of the troponin assay occurred in 44 (51.8%) of the patients with an elevated peak troponin level and constitute the high (+) group. As shown in Table 1, their long-term risk of death was at least 3-fold higher than the remaining patients. Compared with the low (+) and troponin-negative groups, the high (+) troponin group had a higher preoperative cardiac risk index as a result of a greater prevalence of ischemic heart disease and more advanced arterial occlusive disease as noted by a higher rate of tissue loss as the indication for vascular surgery. The preoperative clinical variables that were associated with a higher long-term postoperative risk of death were preoperative cardiac risk, as defined by an RCRI ≥3 risks and advanced arterial

| Table 1 | Clinical predictors and outcomes based on peak postoperative troponin levels |
|-----------------|-----------------------|-----------------------|-----------------------|
| Clinical variables | Negative (n = 79) | Low (+) (n = 41) | High (+) (n = 44) | $P$ |
| **Outcomes** | | | | |
| 1-y Mortality | 1 (1.3) | 3 (7.3) | 10 (22.7) | <.001 |
| 2.5-y Mortality | 5 (6.3) | 7 (17.1) | 20 (45.5) | <.001 |
| **Preoperative variables** | | | | |
| Age (y) | 66.1 ± 7.2 | 68.4 ± 8.5 | 69.9 ± 8.0 | .029 |
| RCRI (≥3 risks) | 20 (25.3) | 15 (36.6) | 26 (59.1) | <.001 |
| Ischemic heart disease | 48 (60.8) | 30 (73.2) | 38 (86) | .019 |
| Congestive heart failure | 8 (10.1) | 4 (9.8) | 13 (29.5) | .009 |
| Cerebrovascular disease | 14 (17.7) | 5 (12.2) | 9 (20.5) | .586 |
| Insulin-dependent diabetes | 13 (16.5) | 9 (22.0) | 15 (34.1) | .080 |
| eGFR <35 | 2 (2.5) | 0 | 2 (4.5) | .397 |
| Ejection fraction (%) | 53.4 ± 11.3 | 55.0 ± 11.8 | 49.2 ± 15.5 | .220 |
| Previous vascular surgery | 23 (29.1) | 8 (19.5) | 18 (40.9) | .096 |
| Hypertension | 65 (82.3) | 36 (87.8) | 38 (86.4) | .684 |
| Hyperlipidemia | 59 (74.7) | 32 (78) | 34 (77.3) | .902 |
| Chronic renal failure | 10 (12.7) | 6 (14.6) | 8 (18.2) | .708 |
| COPD | 12 (15.2) | 6 (14.6) | 10 (22.7) | .506 |
| **Vascular surgical variables** | | | | |
| Urgent/emergent | 8 (10.1) | 1 (2.4) | 7 (15.9) | .111 |
| Tissue loss | 15 (19.0) | 10 (24.4) | 18 (40.9) | .029 |
| Endovascular stent | 20 (25.3) | 12 (29.3) | 6 (13.6) | .191 |
| Open abdominal aortic surgery | 13 (16.5) | 7 (17.1) | 9 (20.5) | .850 |
| Infragenual bypass | 23 (29.1) | 7 (17.1) | 12 (27.3) | .343 |
| Carotid surgery | 14 (17.7) | 7 (17.1) | 2 (4.5) | .106 |
| Amputation | 9 (11.4) | 8 (19.5) | 15 (34.1) | .010 |
| ECG measured postsurgery | 68 (86.1) | 33 (80.5) | 42 (95.5) | .109 |
| ECG (ischemic changes) | 11 (16.2) | 4 (12.1) | 11 (26.2) | .245 |
| Perioperative β-blockers | 61 (77.2) | 30 (73.2) | 39 (88.6) | .176 |
| Preoperative statins | 59 (74.7) | 33 (80.5) | 31 (70.5) | .563 |
| Postoperative statins | 54 (68.4) | 33 (80.5) | 31 (70.5) | .361 |
| Perioperative clopidogrel | 9 (11.4) | 7 (17.1) | 5 (11.4) | .640 |
| Perioperative aspirin | 57 (72.2) | 30 (73.2) | 33 (75) | .943 |

Data are expressed as means ± SD or n (%).

Peak troponins were obtained within 48 hours postsurgery and categorized according to the manufacture’s recommendations based on the URL as negative (<URL), low (+) (≥URL and <3 times URL), or high (+) (≥3 times URL). RCRI assumes that vascular surgery is one risk [8].

COPD indicates chronic obstructive pulmonary disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate.

$^a$ A blinded assessment was made for potential ischemic changes compared with preoperative ECG.

$^b$ Statins were used preoperatively and postoperatively at discharge from the hospital.
occlusive disease, as documented by tissue loss. The postoperative clinical variables that were associated with a higher risk of death were peak troponin levels and lack of use of statins (Figs. 1 and 2). Baseline patient characteristics and surgical variables according to survival status at 2.5 years after the vascular operation are presented in Table 2.

A logistic regression model included the RCRI (≥3 risks), age < mean (67 years), the presenting vascular surgical problem (arterial occlusive disease with clinical evidence of tissue loss), postoperative use of statins, and postoperative peak troponin values (≥3 times the URL). As shown in Fig. 3, the significant independent predictors of long-term postoperative mortality were peak postoperative troponin levels (OR, 8.85; 95% CI, 3.29-23.81; P < .001), tissue loss (OR, 2.87; 95% CI, 1.03-8.00; P = .043), and lack of postoperative use of statins (OR, 0.19; 95% CI, 0.07-0.49; P < .001). Peak troponin values (mean ± 95% confidence intervals) relative to survival at 2.5 years after the vascular operation are shown in Fig. 4.

The receiver operating characteristics curves for discriminating patients who survived versus those who died at 2.5 years were determined for peak troponin levels, postoperative use of statins, and RCRI. The c indexes for all variables are shown in Table 3 and demonstrate that the peak troponin levels outperformed other clinical risk variables for predicting death at 2.5 years after surgery.

3. Discussion

The principal finding of this study is that the peak postoperative troponin levels from consecutive patients...
undergoing vascular operations provide incremental value in predicting long-term outcomes beyond accepted clinical variables used to assess preoperative cardiac and perioperative vascular surgical risks. We found that the optimal peak troponin level for predicting the long-term postoperative risk of death was greater than or equal to 3 times the URL of the specific troponin assay. Although the URL is a predetermined value defined by the manufacturer’s estimate of the 99th percentile of a normal population, a higher threshold may be a more suitable measure for determining outcome in a cohort with a high prevalence of coronary artery disease. A threshold troponin level at greater than or equal to 3 times the URL has been advocated by the Combined Task Forces for the Redefinition of MI among those patients undergoing revascularization with either percutaneous coronary interventions or coronary artery bypass graft surgery [10]. Accordingly, a similar level may be suitable for considering an abnormally high biomarker after vascular surgery. Equally important was our observation that use of statins at the time of discharge was independently associated with a reduction in long-term postoperative mortality and extend previous observations that this class of drugs is protective in the early period after vascular surgery [9,14].

Although an elevated cardiac troponin level above the URL is an identifier of those patients with a poor outcome after vascular operations [4,5], the utility of routine surveillance with troponin assays for providing independent estimates of long-term postoperative outcomes has been uncertain [6]. Patients with vascular disease have at least a 50% probability of having significant coronary artery disease and therefore, comprise a heterogeneous cohort with variable long-term outcomes after surgery [15]. In the CARP registry involving more than 4500 nonrandomized patients, those patients who were excluded because of no cardiac risks had a 12% mortality at 2.5 years after vascular surgery compared with a 23% long-term postoperative mortality in the randomized cohort with documented coronary artery disease.

![Odds Ratio (95% Confidence Intervals; P-Value)](image)

**Fig. 3** Clinical variables that were entered into the logistic regression model are shown and the significant independent predictors of long-term mortality were high peak troponin levels (≥3 times the URL), tissue loss at presentation, and postoperative use of statins at the time of discharge.

![Mean (±95% CI) peak troponin values relative to survival at 2.5 years after the vascular operation (P = .04).](image)

**Fig. 4**

**Table 3** Sensitivity-specificity curves for long-term postoperative risk of death

<table>
<thead>
<tr>
<th>Perioperative clinical variables</th>
<th>c Index</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCRI</td>
<td>0.57</td>
<td>0.49-0.65</td>
<td>.20</td>
</tr>
<tr>
<td>Peak troponin levels</td>
<td>0.75</td>
<td>0.68-0.82</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Postoperative statins</td>
<td>0.66</td>
<td>0.58-0.73</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>
Although patients with significant obstructive coronary artery disease are known to have a higher risk of death both early and late after vascular surgery [16], randomized patients within both the CARP trial and the Decrease-V Pilot Study [17] did not demonstrate a long-term survival benefit with preoperative coronary artery revascularization [18]. Within the CARP trial, the findings from the randomized cohort were generalizable to high-risk clinical subsets, defined by 3 or more revised cardiac risks and an abnormal preoperative stress imaging test [12] as well as high-risk anatomical subsets, defined by 3-vessel coronary artery disease [19]. On the basis of these prospective randomized studies, the recent American College of Cardiology/American Heart Association guidelines do not advocate routine preoperative cardiac workups in the majority of stable patients scheduled for elective vascular surgery [1].

In the absence of sufficient data to justify aggressive interventions in the preoperative period, newer strategies should be devised for risk factor modification in the postoperative period after high-risk noncardiac operations. In a substudy of the CARP trial, in which all patients had serial blood samples drawn after vascular surgery, a peak postoperative troponin value exceeding the URL of the troponin I assay occurred in nearly one third of the patients and was not lower in patients who had undergone preoperative coronary artery revascularization [3]. In that study, the most important predictor of an elevated postoperative troponin level was an aortic cross-clamp procedure, demonstrating that the surgical stress related to the complexity of the vascular operation may be a more important determinant of postoperative outcomes than the extent of preoperative coronary artery disease. Beyond the immediate period after a vascular procedure, it is known that late outcomes are influenced by the nature of the presenting vascular problem, as demonstrated by Krupski and colleagues [13] nearly 2 decades ago. In support of the observations of Krupski et al, outcomes from the CARP registry showed that advanced arterial occlusive disease with tissue loss was a significant predictor of mortality at 2.5 years after vascular surgery, independent of the associated cardiac risks [7]. In the present study, tissue loss with nonhealing at presentation was a borderline significant identifier of poor outcome but less robust as an identifier of outcome than the peak postoperative troponin levels. These data demonstrate that when correcting for preoperative cardiac risks and the extent of advanced arterial occlusive disease on presentation, perioperative cardiac biomarkers remain the predominant identifier of long-term outcome.

Although preoperative cardiac interventions do not improve long-term postoperative outcomes, the addition of pharmacological interventions before vascular surgery is an important consideration. Administration of β-blockers before vascular surgery reduces postoperative cardiac complications [20,21], and these drugs were used in nearly 80% of patients in the present cohort. It is not clear why all patients did not receive this therapy, but the protective effect of β-blockers may not be robust in all high-risk subsets undergoing noncardiac operations, particularly those individuals who may present with significant cerebrovascular disease [22]. Statins may have more promise for preserving at least short-term postoperative outcomes, as shown in both retrospective and prospective analyses [9,14]. In the present cohort, statins were used in the postoperative period in 141 (86.0%) of the patients, which was higher than the expected based on the prevalence of coronary artery disease in a heterogeneous group of patients undergoing vascular surgery [15]. When considering emerging evidence of proven benefit in the short-term postoperative period in the majority of patients, however, this may represent an underutilization of a therapy with proven benefit. An analysis of long-term outcomes after vascular surgery has shown that therapies with proven benefit are underutilized in patients with vascular disease on long-term follow-up [23]. The present study is supportive of this observation and shows that use of statins after vascular surgery is a significant predictor of long-term postoperative outcome, independent of standard cardiac and vascular surgical risks.

3.1. Limitations

The population enrolled in this study is predominantly male. Although the proposed model for risk prediction only contains 3 variables, the possibility of over fitting should be considered given the relatively small number of observations. The predictive performance of these variables needs to be validated in different data sets.

3.2. Conclusions

In a heterogeneous group of patients undergoing vascular surgery, perioperative peak troponin values and use of statins were significant independent predictors of long-term postoperative outcomes, when considering preoperative cardiac risks and presenting vascular surgical characteristics. Future studies should address whether additional strategies for risk factor modification in the postoperative period might improve outcomes in this high-risk cohort.

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References


